update Search 4/03

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     (FILE 'HOME' ENTERED AT 12:44:56 ON 12 NOV 2003)

     FILE 'CAPLUS, USPATFULL' ENTERED AT 12:45:05 ON 12 NOV 2003
L1          6239 FILE CAPLUS
L2         20895 FILE USPATFULL
     TOTAL FOR ALL FILES
L3         27134 S WRINKLE
L4             2 FILE CAPLUS
L5             3 FILE USPATFULL
     TOTAL FOR ALL FILES
L6             5 S FIBROBLAST (5A) BIOSYNTHESIS (5A) EXCESSIVE
L7           352 FILE CAPLUS
L8            47 FILE USPATFULL
     TOTAL FOR ALL FILES
L9           399 S FIBROBLAST (5A) BIOSYNTHESIS
L10            0 FILE CAPLUS
L11            9 FILE USPATFULL
     TOTAL FOR ALL FILES
L12            9 S L9 AND  L3
L13           47 FILE CAPLUS
L14          704 FILE USPATFULL
     TOTAL FOR ALL FILES
L15          751 S ((HYPERTOPHIC WOUND) OR SCAR) AND  L3
L16           26 FILE CAPLUS
L17          360 FILE USPATFULL
     TOTAL FOR ALL FILES
L18          386 S ((HYPERTOPHIC WOUND) OR SCAR) (1S)  L3
L19            0 FILE CAPLUS
L20            6 FILE USPATFULL
     TOTAL FOR ALL FILES
L21            6 S L18 AND (MYOFIBROBLAST)
L22            4 FILE CAPLUS
L23          194 FILE USPATFULL
     TOTAL FOR ALL FILES
L24          198 S (MINOXIDIL (1S) CALCIUM CHANNEL)
L25            0 FILE CAPLUS
L26           10 FILE USPATFULL
     TOTAL FOR ALL FILES
L27           10 S L15 AND (MYOFIBROBLAST)
L28            0 FILE CAPLUS
L29            4 FILE USPATFULL
     TOTAL FOR ALL FILES
L30            4 S (L27 (1S) CALCIUM CHANNEL)

=> save l09981751/l
ENTER L#, L# RANGE, ALL, OR (END):all
L# LIST L1-L30 HAS BEEN SAVED AS 'L09981751/L'

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L12 ANSWER 7 OF 9 USPATFULL on STN

SUMM In the final, remodeling phase (stage III), the previously constructed and randomly organized matrix is remodeled into an organized structure which is highly cross-linked and aligned to maximize mechanical strength. Natural skin **wrinkles** (relaxed skin tension lines) which align themselves in the direction of mechanical tension and become permanent on the face over time are a common manifestation of this control process. With hypertrophic scars and keloids, the biosynthetic phase continues longer than necessary to repair the wound. In order to maintain nutrient supply in these scars, vascular in-growth occurs, resulting in a large, highly vascularized scar which is unsightly and can be disabling.

DETD A method of the present invention utilizes the discovery that calcium antagonists, which interfere with calcium metabolism or transport across the cell membrane, can inhibit exocytosis in **fibroblast** cells; can retard **biosynthesis** of collagen and sulfated glycosaminoglycans (GAG); can be used to decrease the collagen content of the extracellular matrix; and can also stimulate increased collagenase activity, leading to softening of the scar tissue. These features work together to control wound scar production; by minimizing, preventing or reversing the scarring process, depending upon the course of the disease or type of wound treated.

DETD Calcium antagonists also regulate cell shape. As described in detail in the Examples, fibroblasts that have been treated with a calcium antagonist became more rounded than untreated fibroblasts. The treated cells were tested for viability and were found to have intact cell membranes which are indicative of viable cells. The observation that treated fibroblast cells become altered was correlated with changes in cell programming from a biosynthetic mode (mechanism normally undertaken by untreated fibroblasts) to a degradative mode. It is believed that this change toward matrix degradation, mediated by cell shape changes, plays a roll in controlling wound scar production. Thus, other compounds can be studied for their ability to regulate (up regulate or down regulate) **fibroblast biosynthesis** by observing their interaction with calcium antagonists.

ACCESSION NUMBER: 96:80033 USPATFULL
TITLE: Method for improvement of scar size and appearance
INVENTOR(S): Lee, Raphael C., Chicago, IL, United States
PATENT ASSIGNEE(S): Arch Development Corporation, Chicago, IL, United States (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 5552162		19960903	
APPLICATION INFO.:	US 1993-15216		19930209	(8)

DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Dees, Jose G.
ASSISTANT EXAMINER: Barts, Samuel
LEGAL REPRESENTATIVE: Arnold White & Durkee
NUMBER OF CLAIMS: 13
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 14 Drawing Figure(s); 9 Drawing Page(s)
LINE COUNT: 1126
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L21 ANSWER 5 OF 6 USPATFULL on STN

SUMM The growth factor-supplemented TSs of this invention are useful for promoting the healing of wounds, especially those that do not readily heal, such as skin ulcers in diabetic individuals, and for delivering growth factors including, but not limited to, FGF-1, FGF-2, FGF-4, PDGFs, EGFs, IGFs, PDGF-bb, BMP-1, BMP-2, OP-1, TGF-.beta., cartilage-inducing factor-A (CIF-A), cartilage-inducing factor-B (CIF-B), osteoid-inducing factor (OIF), angiogenin(s), endothelins, hepatocyte growth factor and keratinocyte growth factor, and providing a medium for prolonged contact between a wound site and the growth factor(s). The growth factor-supplemented TS may be used to treat burns and other skin wounds and may comprise a TS and, in addition to the growth factor(s), an antibiotic(s) and/or an analgesic(s), etc. The growth factor-supplemented TS may be used to aid in the engraftment of a natural or artificial graft, such as skin to a skin wound. They may also be used cosmetically, for example in hair transplants, where the TS might contain FGF, EGF, antibiotics and minoxidil, as well as other compounds. An additional cosmetic use for the compositions of this invention is to treat **wrinkles** and **scars** instead of using silicone or other compounds to do so. In this embodiment, for example, the TS may contain FGF-1, FGF-4, and/or PDGFs, and fat cells. The growth factor-supplemented TSs may be applied to surgical wounds, broken bones or gastric ulcers and other such internal wounds in order to promote healing thereof. The TSs of this invention may be used to aid the integration of a graft, whether artificial or natural, into an animal's body as for example when the graft is composed of natural tissue. The TSs of this invention can be used to combat some of the major problems associated with certain conditions such as periodontitis, namely persistent infection, bone resorption, loss of ligaments and premature re-epithelialization of the dental pocket.

DETD Untreated controls (A & B) showed minimal mesenchymal tissue ingrowth, with both their interstices filled with, and their luminal surfaces coated with fibrin coagulum. The FG-treated grafts showed mesenchymal tissue ingrowth in only the outer half of the grafts' interstices, with the rest being filled with fibrin coagulum. Very few interstitial capillaries were present. In contrast, the grafts treated with FG containing FGF-1 showed more abundant interstitial ingrowth and by 28 days showed numerous capillaries, **myofibroblasts** and macrophages, with inner capsules consisting of several layers of **myofibroblasts** beneath confluent endothelial cell layers. Results of similar grafts after 128 days of implantation were similar, with greater numbers of capillaries in the FG +FGF-1 group (data not shown).

ACCESSION NUMBER: 2000:121069 USPATFULL

TITLE: Supplemented and unsupplemented tissue sealants, method of their production and use

INVENTOR(S): MacPhee, Martin James, Gaithersburg, MD, United States
Drohan, William Nash, Springfield, VA, United States
Liau, Gene, Darnestown, MD, United States
Haudenschild, Christian, Rockville, MD, United States

PATENT ASSIGNEE(S): The American National Red Cross, Falls Church, VA, United States (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 6117425		20000912
APPLICATION INFO.:	US 1995-474086		19950607 (8)

RELATED APPLN. INFO.: Continuation-in-part of Ser. No. US 1994-351006, filed on 7 Dec 1994, now abandoned which is a continuation-in-part of Ser. No. US 1994-328552, filed on 25 Oct 1994, now abandoned which is a continuation of Ser. No. US 1993-31164, filed on 12 Mar 1993, now

abandoned which is a continuation-in-part of Ser. No. US 1990-618419, filed on 27 Nov 1990, now abandoned which is a continuation-in-part of Ser. No. US 1991-798919, filed on 27 Nov 1991, now abandoned
DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Woodward, M Patrick
ASSISTANT EXAMINER: Zeman, Mary K
LEGAL REPRESENTATIVE: Sterne, Kessler Goldstein & Fox P.L.L.C.

L30 ANSWER 4 OF 4 USPATFULL on STN

SUMM Growth factors are, therefore, potentially useful for specifically promoting wound healing and tissue repair. However, their use to promote wound healing has yielded inconsistent results (see, e.g., Carter et al., in Growth Factors and Other Aspects of Wound Healing: Biological and Clinical Implications, Alan R. Liss, Inc., New York, N.Y., pp. 303-317 (1988)). For example, PDGF, IGF-1, EGF, TGF-.alpha.,TGF-.beta. and FGF (also known as HBGF) applied separately to standardized skin wounds in swine had little effect on the regeneration of connective tissue or epithelium in the wounds (Lynch et al., J. Clin. Invest. 84:640-646 (1989)). Of the factors tested, TGF-.beta. stimulated the greatest response alone. However, a combination of factors, such as PDGF-bb homodimer and IGF-1 or TGF-.alpha. produced a dramatic increase in connective tissue regeneration and epithelialization. (Id.) Tsuboi et al. have reported that the daily application of bFGF to an open wound stimulated wound healing in healing-impaired mice but not in normal mice (J. Exp. Med. 172:245-251 (1990)). On the other hand, the application to human skin wounds of crude preparations of porcine or bovine platelet lysate, which presumably contained growth factors, increased the rate at which the wounds closed, the number of cells in the healing area, the growth of blood vessels, the total rate of collagen deposition and the strength of the **scar** tissue (Carter et al., supra).

SUMM The growth factor-supplemented TSs of this invention are useful for promoting the healing of wounds, especially those that do not readily heal, such as skin ulcers in diabetic individuals, and for delivering growth factors including, but not limited to, FGF-1, FGF-2, FGF-4, PDGFs, EGFs, IGFs, PDGF-bb, BMP-1, BMP-2, OP-1, TGF-.beta., cartilage-inducing factor-A (CIF-A), cartilage-inducing factor-B (CIF-B), osteoid-inducing factor (OIF), angiogenin(s), endothelins, hepatocyte growth factor and keratinocyte growth factor, and providing a medium for prolonged contact between a wound site and the growth factor(s). The growth factor-supplemented TS may be used to treat burns and other skin wounds and may comprise a TS and, in addition to the growth factor(s), an antibiotic(s) and/or an analgesic(s), etc. The growth factor-supplemented TS may be used to aid in the engraftment of a natural or artificial graft, such as skin to a skin wound. They may also be used cosmetically, for example in hair transplants, where the TS might contain FGF, EGF, antibiotics and minoxidil, as well as other compounds. An additional cosmetic use for the compositions of this invention is to treat **wrinkles** and **scars** instead of using silicone or other compounds to do so. In this embodiment, for example, the TS may contain FGF-1, FGF4, and/or PDGFs, and fat cells. The growth factor-supplemented TSs may be applied to surgical wounds, broken bones or gastric ulcers and other such internal wounds in order to promote healing thereof. The TSs of this invention may be used to aid the integration of a graft, whether artificial or natural, into an animal's body as for example when the graft is composed of natural tissue. The TSs of this invention can be used to combat some of the major problems associated with certain conditions such as periodontitis, namely persistent infection, bone resorption, loss of ligaments and premature re-epithelialization of the dental pocket.

DRWD Untreated controls (A & B) showed minimal mesenchymal tissue ingrowth, with both their interstices filled with, and their luminal surfaces coated with fibrin coagulum. The FG-treated grafts showed mesenchymal tissue ingrowth in only the outer half of the grafts' interstices, with the rest being filled with fibrin coagulum. Very few interstitial capillaries were present. In contrast, the grafts treated with FG containing FGF-1 showed more abundant interstitial ingrowth and by 28 days showed numerous capillaries, **myofibroblasts** and macrophages, with inner capsules consisting of several layers of **myofibroblasts** beneath confluent endothelial cell layers. Results of similar grafts after 128 days of implantation were similar,

with greater numbers of capillaries in the FG+FGF-1 group (data not shown).

DETD The supplemented TS of the present invention may contain compounds such as drugs, other chemicals, and proteins. These may include, but are not limited to: antibiotics such as TET, ciprofloxacin, amoxicillin, or metronidazole, anticoagulants, such as activated protein C, heparin, prostracyclin (PGI.sub.2), prostaglandins, leukotrienes, antithrombin III, ADPase, and plasminogen activator; steroids, such as dexamethasone, inhibitors of prostacyclin, prostaglandins, leukotrienes and/or kinins to inhibit inflammation; cardiovascular drugs, such as **calcium channel** blockers; chemoattractants; local anesthetics such as bupivacaine; and antiproliferative/antitumor drugs such as 5-fluorouracil (5-FU), taxol and/or taxotere. These supplemental compounds may also include polyclonal, monoclonal or chimeric antibodies, or functional derivatives or fragments thereof. They may be antibodies which, for example, inhibit smooth muscle proliferation, such as antibodies to PDGF, and/or TGF-.beta., or the proliferation of other undesirable cell types within and about the area treated with the TS. These antibodies can also be useful in situations where anti-cancer, anti-platelet or anti-inflammatory activity is needed. In general, any antibody whose efficacy would be improved by site-directed delivery may benefit from being used with this TS delivery system.

DETD The drug may be an analgesic, antiseptic, antibiotic or other drug(s), such as antiproliferative drugs which can inhibit infection, promote wound healing and/or inhibit **scar** formation. More than one drug may be added to the composition, to be released simultaneously, or the drug may be released in predetermined time-release manner. Such drugs may include, for example, taxol, tetracycline free base, tetracycline hydrochloride, ciprofloxacin hydrochloride or 5-fluorouracil. The addition of taxol to the fibrin sealant complex may be particularly advantageous. Further, the drug may be a vasoconstrictor, e.g., epinephrine; or the drug may be added to stabilize the tissue sealant or fibrin clot, e.g., aprotinin. The supplement(s) is at a concentration in the TS such that it will be effective for its intended purpose, e.g., an antibiotic will inhibit the growth of microbes, an analgesic will relieve pain, etc.

DETD Each slide was given a histological score ranging from 1 to 15, with 1 corresponding to no healing and 15 corresponding to a **scar** with organized collagen fibers (Table 2). The scoring scale was based on scales used by previous investigators. The criteria used previously were modified and were further defined to more precisely reflect the extent of: reepithelialization, degree of cellular invasion, granulation tissue formation, collagen deposition, vascularity, and wound contraction. The histologic score was assigned

DETD This embodiment is a self-contained TS wound dressing, or bandage, which contains both the thrombin and fibrinogen components of the FG. The calcium is contained in either the thrombin and/or the fibrinogen component(s). Either or both of the thrombin or fibrinogen components can be, but does not have to be, supplemented with a growth factor(s), such as a FGF or bFGF, or a drug(s) such as, an analgesic, antibiotic or other drug(s), which can inhibit infection, promote wound healing and/or inhibit **scar** formation. The supplement(s) is at a concentration in the TS such that it will be effective for its intended purpose, e.g., an antibiotic will inhibit the growth of microbes, an analgesic will relieve pain.

ACCESSION NUMBER: 2000:50372 USPATFULL

TITLE: Supplemented and unsupplemented tissue sealants, methods of their production and use

INVENTOR(S): MacPhee, Martin James, Gaithersburg, MD, United States
Drohan, William Nash, Springfield, VA, United States
Woolverton, Christoper J., Kent, OH, United States

PATENT ASSIGNEE(S): The American National Red Cross, Washington, DC, United States (U.S. government)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 6054122		20000425
APPLICATION INFO.:	US 1995-479034		19950607 (8)

RELATED APPLN. INFO.: Continuation-in-part of Ser. No. US 1994-351006, filed on 7 Dec 1994, now abandoned which is a continuation-in-part of Ser. No. US 1994-328552, filed on 25 Oct 1994, now abandoned which is a continuation of Ser. No. US 1993-31164, filed on 12 Mar 1993, now abandoned which is a continuation-in-part of Ser. No. US 1990-618419, filed on 27 Nov 1990, now abandoned And a continuation-in-part of Ser. No. US 1991-798919, filed on 27 Nov 1991, now abandoned

DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Smith, Lynette F.
ASSISTANT EXAMINER: Zeman, Mary K
LEGAL REPRESENTATIVE: Sterne, Kessler, Goldstein & Fox P.L.L.C.
NUMBER OF CLAIMS: 43
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 50 Drawing Figure(s); 36 Drawing Page(s)
LINE COUNT: 4855
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

Untreated controls (A & B) showed minimal mesenchymal tissue ingrowth, with both their interstices filled with, and their luminal surfaces coated with fibrin coagulum. The FG-treated grafts showed mesenchymal tissue ingrowth in only the outer half of the grafts' interstices, with the rest being filled with fibrin coagulum. Very few interstitial capillaries were present. In contrast, the grafts treated with FG containing FGF-1 showed more abundant interstitial ingrowth and by 28 days showed numerous capillaries, **myofibroblasts** and macrophages, with inner capsules consisting of several layers of **myofibroblasts** beneath confluent endothelial cell layers. Results of similar grafts after 128 days of implantation were similar, with greater numbers of capillaries in the FG +FGF-1 group (data not shown).

DETD The supplemented TS of the present invention may contain compounds such as drugs, other chemicals, and proteins. These may include, but are not limited to: antibiotics such as TET, ciprofloxacin, amoxicillin, or metronidazole, anticoagulants, such as activated protein C, heparin, prostracyclin (PG.sub.2), prostaglandins, leukotrienes, antithrombin III, ADPase, and plasminogen activator; steroids, such as dexamethasone, inhibitors of prostacyclin, prostaglandins, leukotrienes and/or kinins to inhibit inflammation; cardiovascular drugs, such as **calcium channel** blockers; chemoattractants; local anesthetics such as bupivacaine; and antiproliferative/antitumor drugs such as 5-fluorouracil (5-FU), taxol and/or taxotere. These supplemental compounds may also include polyclonal, monoclonal or chimeric antibodies, or functional derivatives or fragments thereof. They may be antibodies which, for example, inhibit smooth muscle proliferation, such as antibodies to PDGF, and/or TGF-.beta., or the proliferation of other undesirable cell types within and about the area treated with the TS. These antibodies can also be useful in situations where anti-cancer, anti-platelet or anti-inflammatory activity is needed. In general, any antibody whose efficacy would be improved by site-directed delivery may benefit from being used with this TS delivery system.

DETD The drug may be an analgesic, antiseptic, antibiotic or other drug(s), such as antiproliferative drugs which can inhibit infection, promote wound healing and/or inhibit **scar** formation. More than one drug may be added to the composition, to be released simultaneously, or the drug may be released in predetermined time-release manner. Such drugs may include, for example, taxol, tetracycline free base, tetracycline hydrochloride, ciprofloxacin hydrochloride or 5-fluorouracil. The addition of taxol to the fibrin sealant complex may be particularly advantageous. Further, the drug may be a vasoconstrictor, e.g., epinephrine; or the drug may be added to stabilize the tissue sealant or fibrin clot, e.g., aprotinin. The supplement(s) is at a concentration in the TS such that it will be effective for its intended purpose, e.g., an antibiotic will inhibit the growth of microbes, an analgesic will relieve pain, etc.

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purpose, e.g., an antibiotic will inhibit the growth of microbes, an analgesic will relieve pain.

ACCESSION NUMBER: 2000:121069 USPATFULL

TITLE: Supplemented and unsupplemented tissue sealants, method of their production and use

INVENTOR(S): MacPhee, Martin James, Gaithersburg, MD, United States
Drohan, William Nash, Springfield, VA, United States
Liau, Gene, Darnestown, MD, United States
Haudenschild, Christian, Rockville, MD, United States

PATENT ASSIGNEE(S): The American National Red Cross, Falls Church, VA, United States (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 6117425		20000912
APPLICATION INFO.:	US 1995-474086		19950607 (8)

RELATED APPLN. INFO.: Continuation-in-part of Ser. No. US 1994-351006, filed on 7 Dec 1994, now abandoned which is a continuation-in-part of Ser. No. US 1994-328552, filed on 25 Oct 1994, now abandoned which is a continuation of Ser. No. US 1993-31164, filed on 12 Mar 1993, now abandoned which is a continuation-in-part of Ser. No. US 1990-618419, filed on 27 Nov 1990, now abandoned which is a continuation-in-part of Ser. No. US 1991-798919, filed on 27 Nov 1991, now abandoned

DOCUMENT TYPE: Utility

FILE SEGMENT: Granted

PRIMARY EXAMINER: Woodward, M Patrick

ASSISTANT EXAMINER: Zeman, Mary K

mprise a TS and, in addition to the growth factor(s), an antibiotic(s) and/or an analgesic(s), etc. The growth factor-supplemented TS may be used to aid in the engraftment of a natural or artificial graft, such as skin to a skin wound. They may also be used cosmetically, for example in hair transplants, where the TS might contain FGF, EGF, antibiotics and minoxidil, as well as other compounds. An additional cosmetic use for the compositions of this invention is to treat **wrinkles** and **scars** instead of using silicone or other compounds to do so. In this embodiment, for example, the TS may contain FGF-1, FGF-4, and/or PDGFs, and fat cells. The growth factor-supplemented TSs may be applied to surgical wounds, broken bones or gastric ulcers and other such internal wounds in order to promote healing thereof. The TSs of this invention may be used to aid the integration of a graft, whether artificial or natural, into an animal's body as for example when the graft is composed of natural tissue. The TSs of this invention can be used to combat some of the major problems associated with certain conditions such as periodontitis, namely persistent infection, bone resorption, loss of ligaments and premature re-epithelialization of the dental pocket.

DRWD Untreated controls (A & B) showed minimal mesenchymal tissue ingrowth, with both their interstices filled with, and their luminal surfaces coated with fibrin coagulum. The FG-treated grafts showed mesenchymal tissue ingrowth in only the outer half of the grafts' interstices, with the rest being filled with fibrin coagulum. Very few interstitial capillaries were present. In contrast, the grafts treated with FG containing FGF-1 showed more abundant interstitial ingrowth and by 28 days showed numerous capillaries, **myofibroblasts** and macrophages, with inner capsules consisting of several layers of **myofibroblasts** beneath confluent endothelial cell layers. Results of similar grafts after 128 days of implantation were similar, with greater numbers of capillaries in the FG+FGF-1 group (data not shown).

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hyperdictionary

EXOCYTOSIS

Biology Dictionary

Definition: Process by which cellular material is discharged from a cell. Compare endocytosis.

exocytosis

<cell biology> Release of material from the cell by fusion of a membrane bounded vesicle with the plasma membrane.

(18 Nov 1997)

Previous: exocrine pancreatic insufficiency, exocrine part of pancreas, exocyclic
Next: exocytotic vesicle, exodeoxyribonuclease, exodeoxyribonucleases